Extension of survival by resection of asynchronous renal cell carcinoma metastases to mediastinal lymph nodes

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Objective: The aim of this study was to determine whether or not resection of isolated mediastinal lymph node renal cell carcinoma metastases confers a survival advantage, as compared with patients with stage IV disease.

Patients and Methods: We retrospectively reviewed the charts of all patients with renal cell carcinoma whose histologic specimens were evaluated at our institution from January 1, 2000, through December 31, 2006. Using Kaplan–Meier estimates, we compared the survival of patients who underwent resection of asynchronous mediastinal lymph node metastases with that of patients with stage IV disease.

Results: During the 7-year study period, of the 386 patients with renal cell carcinoma who were evaluated at our institution, 9 underwent resection of asynchronous mediastinal lymph node metastases. After primary tumor resection and before diagnosis of asynchronous mediastinal lymph node metastases, all patients completed chemotherapy, cytokine therapy, or tumor vaccination; 3 underwent radiotherapy. The median age at resection of mediastinal lymph nodes was 57.7 years (range, 39.7–81.2). The median time from primary tumor resection to mediastinal lymph node resection was 2.8 years (range, 0.5–23.3). In all, 4 patients underwent resection of metastases via thoracotomy and 5, via thoracoscopy. The median number of mediastinal lymph nodes pathologically evaluated was 7 (range, 2–28); the median number of positive mediastinal lymph nodes per patient was 1.5 (range, 1–3). We found no surgical complications. The median survival after resection of metastases (3.2 years) was significantly longer ($P = .021$) than for other patients with stage IV disease at our institution (1.1 years).

Conclusions: Resection of renal cell carcinoma mediastinal lymph node metastases is safe, appears to extend survival, and should be considered an important component of treating patients with renal cell carcinoma who have asynchronous mediastinal lymph node metastases.

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In 2007, about 51,190 persons in the United States will be diagnosed with renal cell carcinoma (RCC) and 12,890 will die of it. Among incident cases, 45% present as localized disease (American Joint Committee on Cancer[1] stage I or II), 25% present as locally advanced disease (stage III), and 30% present with metastatic disease (stage IV).

Abbreviations and Acronyms
IL-2 = interleukin 2
MLN = mediastinal lymph node
RCC = renal cell carcinoma

Patients with asynchronous RCC metastases have a more favorable prognosis (median survival, 21 months)[2] than those with synchronous metastases (median survival, 10 months).[3] Resection of synchronous metastases does not impart a survival advantage.[4] However, resection of isolated abdominal and pulmonary parenchymal asynchronous metastases results in a more favorable prognosis.[4-7]

In the treatment of patients with RCC with recurrent or advanced disease, the systemic medical therapies used are wide and of limited efficacy. When we began seeing patients with isolated mediasinal lymph node (MLN) metastases, we began offering surgical resection as therapy because of the isolated nature of their disease recurrence and the efficacy of current medical therapies available. We could find no published reports on the efficacy or possible survival advantage of resecting isolated asynchronous MLN metastases in patients with RCC. Traditionally, such patients have been treated with either palliative or experimental chemotherapy.

The aim of this study was to determine whether patients with RCC who undergo resection of isolated asynchronous MLN metastases have a survival advantage as compared with other patients having stage IV disease.

Methods

Data Collection

The University of Minnesota Institutional Review Board approved this study and waived the need for informed consent. Using a database prospectively maintained by the Department of Laboratory Medicine and Pathology (J.J.), we retrospectively reviewed the charts of all patients with RCC whose histologic specimens were evaluated at our institution from January 1, 2000, through December 31, 2006. By cross-referencing this dataset with the Section of Thoracic and Foregut Surgery database (M.A.M., R.S.A.), we identified patients with RCC who underwent resection of isolated asynchronous MLN metastases at our institution (study cohort). We collected data on patient characteristics, comorbidities, perioperative details, neoadjuvant and adjuvant therapy, tumor characteristics, and survivals.

To establish a control group for comparison with our study cohort, we used the University of Minnesota Cancer Center Registry to collect data (eg, patient characteristics, tumor stage, survival) on all patients with RCC treated at our institution.

Statistical Analysis

For statistical analyses, we used JMP for Windows, version 4.0.4 (SAS Institute, Inc, Cary, NC). Data are reported as mean ± standard deviation unless otherwise noted. For between-group comparisons of ordinal and nominal variables, we used a χ^2 test ($\alpha = .05$); for continuous variables, we used a t test ($\alpha = .05$). For survival analyses, two survival times were used. The first was the overall survival time, from the time of diagnosis, defined as the time from diagnosis to death or last available follow-up (for those patients with both resectable and unresectable disease). The second survival time employed was the postresection survival time, from the time of resection, defined as the time from surgical resection to death or last available follow-up (as recorded in the University of Minnesota Cancer Center Registry at the time of initial manuscript submission). For survival analyses, we used the Kaplan–Meier method. To compare survival functions, we used a log–rank test ($\alpha = .05$).

Results

Patient Characteristics

Over the 7-year study period, the Department of Laboratory Medicine and Pathology evaluated 386 cases of RCC. Of

TABLE 1. Patient and tumor characteristics (study cohort)

Patient	Sex	Initial stage*	Age at metastasectomy (y)	Time to MLN metastasectomy (y)	Time from initial diagnosis to last follow-up (y)	Time from MLN metastasectomy to last follow-up (y)	Surgical approach	MLN size (cm)	Motzer score†	Fuhrman grade‡	Angiolymphatic invasion
1	M	III	61	7.3	10.1	2.8	V	3.7	0	2	Yes
2	M	III	81	23.3	23.5	0.2	T	4.2	0	2	Yes
3	M	I	69	5.4	8.2	2.7	V	0.8	1	3	Yes
4	M	I	59	0.7	3.9	3.2	T	2.8	0	2	Yes
5	F	III	52	4.5	5.7	1.2	T	3	0	2	Yes
6	F	III	40	0.5	1.1	0.6	T	2.5	0	3	Yes
7	M	IV	50	2.8	3.9	1.1	V	7.6	0	3	Yes
8	M	III	58	1	2.8	1.8	V	3.9	0	3	Yes
9	M	III	54	0.7	1.8	1.2	V	5	0	3	Yes

V, Video-assisted thoracoscopic surgery; *T,* thoracotomy; *M,* male; *F,* female; *MLN,* mediastinal lymph node. *Stage based on American Joint Committee on Cancer criteria.[1] †Motzer score is the sum of the number of the following risk factors: hemoglobin ≤ 13 g/dL (male) or ≤ 11.5 g/dL (female), a corrected calcium > 10 mg/dL, and a Karnofsky performance status < 80%.[3] ‡Fuhrman grade of 1 through 4, based on increasing nuclear size, cellular irregularity and nucleolar prominence.[8]

TABLE 2. Sequence of treatment

Patient			First-line therapy		Second-line therapy		Third-line therapy	Fourth-line therapy	Fifth-line therapy	Alive
1	Nephrectomy	Metastasectomy	Sunitinib							Yes
2	Nephrectomy	Metastasectomy	None							Yes
3	Nephrectomy	Metastasectomy	None							Yes
4*	Nephrectomy		HD IL-2	Metastasectomy	LMI vaccine		852-A m-toll agonist	Suramin and 5-FU	Cetuximab	No
5*	Nephrectomy		LMI vaccine		Sunitinib	Metastasectomy	Sorafenib			Yes
6	Nephrectomy		LMI vaccine	Metastasectomy	HD IL2					Yes
7*	Nephrectomy		LMI vaccine	Metastasectomy	Sorafenib					Yes
8	Nephrectomy		HD IL-2		Sorafenib	Metastasectomy	Sunitinib			Yes
9	Nephrectomy	Metastasectomy	Bevacizumab							Yes

HD IL-2, High-dose interleukin 2; *5-FU,* 5-fluorouracil; *LMI,* large multivalent immunogen; *Denotes radiation therapy.

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those 386 patients, 9 underwent resection of isolated asynchronous MLN metastases (Table 1). All 9 patients had undergone radical nephrectomy before MLN metastases developed (Table 2); at that time, 6 had stage III disease. The 1 patient with stage IV disease had an isolated humerus metastasis that was treated with (and responded to) radiation therapy. The median age at resection of MLN metastases was 57.7 years (range, 39.7–81.2), and the median interval from primary tumor resection to metastasectomy was 2.8 years (range, 0.5–23.3). New MLN metastases were identified during routine surveillance, as part of the evaluation for other procedures, or incidentally. Selected images (Figure 1) from a fusion positron emission tomography/computed tomography scan show increased metabolic activity within the mediastinum of 1 patient with MLN metastases.

Comorbidities

In general, the study cohort had minimal comorbidities. There were the following conditions: hypertension (n = 4), gastroesophageal reflux disease (n = 3), coronary artery disease (n = 2), type 2 diabetes mellitus (n = 2), chronic obstructive pulmonary disease (n = 1), tobacco use (n = 2), asthma (n = 1), and chronic renal insufficiency (creatinine >1.5 mg/dL) (n = 0).

Perioperative Details

Of the 9 patients who underwent resection of MLN metastases, 5 underwent thoracoscopy and 4, thoracotomy. Blood loss was minimal (range, 25–250 mL). The median operative time was 210 minutes (range, 120–270 minutes). The median number of MLNs pathologically evaluated was 7 (range 2–28). Of those MLNs, a median of 1.5 (range, 1–3) were positive for metastatic RCC, per our final pathologic examination. The median largest dimension of the histologically positive MLN was 3.7 cm (range, 0.8–7.6).

The mean postoperative hospital length of stay was 4.1 ± 3.3 days. Duration of chest tube placement was 2.9 ± 2.1 days. There were no perioperative deaths. The only complication was related to chemotherapy: upper gastrointestinal bleeding (diffuse gastritis on esophagogastroduodenoscopy) in 1 patient resulted in acute blood loss anemia and the need

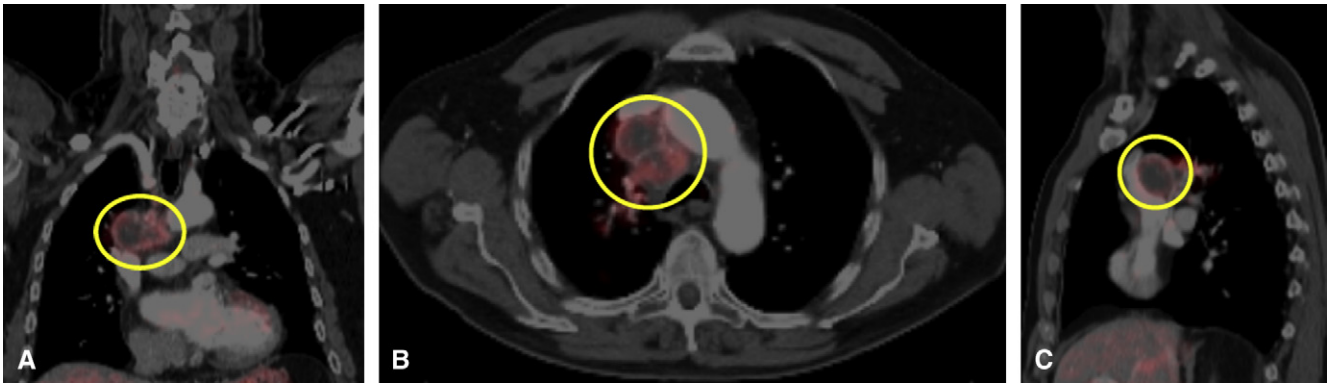

Figure 1. Fusion positron emission tomography/computed tomography scan of an isolated RCC metastasis to station 4R (per American Thoracic Society) MLN *(circled):* coronal (A), axial (B), and sagittal (C) views. *RCC,* Renal cell carcinoma; *MLN,* mediastinal lymph node.

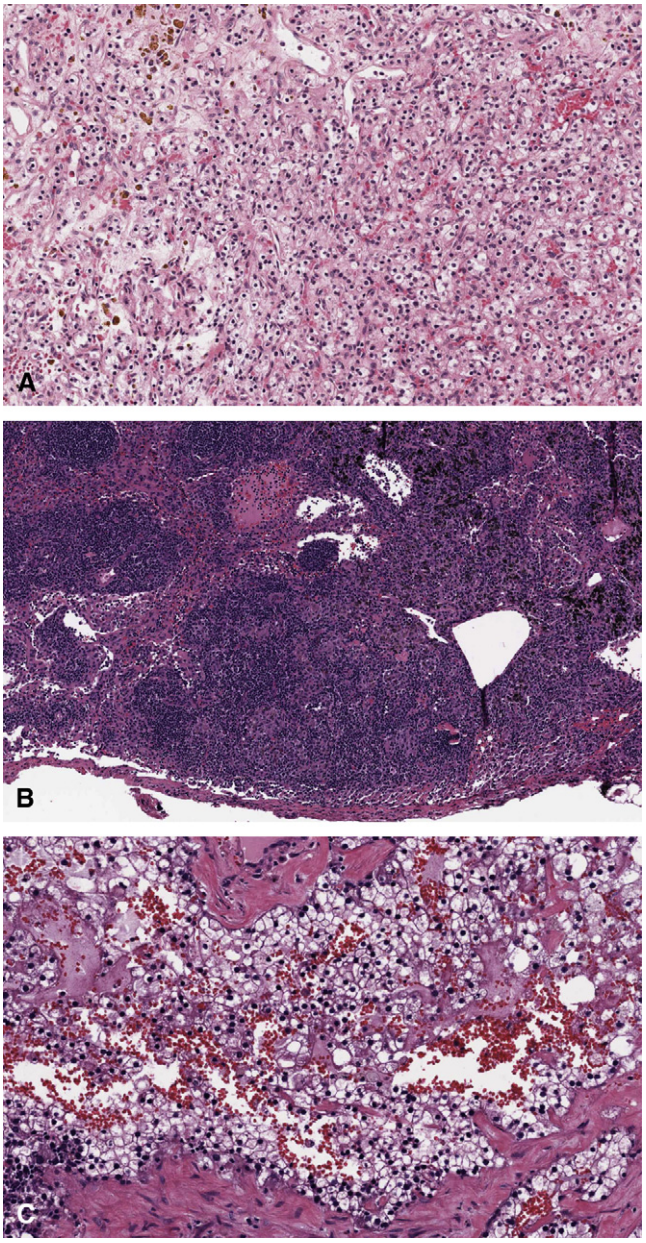

Figure 2. Hematoxylin and eosin histologic slide of a primary RCC in the kidney, clear variant with a Fuhrman nuclear grade of 1 (A), a normal MLN without metastasis (B), and an MLN with isolated asynchronous RCC metastasis, clear cell variant, with a Fuhrman nuclear grade of 2 (C). *RCC,* Renal cell carcinoma; *MLN,* mediastinal lymph node.

for blood transfusion. The mean survival time after resection of MLN metastases was 3.9 years. The median time after resection was more than 3.2 years (range, 2.8–>3.2 years); of our 9 study cohort patients, at the end of the 7-year study period, 1 had died, 1 had been lost to follow-up, and 7 were alive and well (Table 2).

Neoadjuvant and Adjuvant Therapies

Our 9 study cohort patients completed a variety of neoadjuvant and adjuvant treatment regimens (Table 2): 4 received a large multivalent immunogen vaccine; 3, high-dose interleukin 2 (IL-2); 3, radiation therapy; 3, sunitinib (Sutent; Pfizer Oncology, New York, NY); 3, sorafenib (Nexavar; Onyx Pharmaceuticals, Inc, Emeryville, Calif); 1, cetuximab (Erbitux; ImClone Systems Inc, New York, NY); 1, bevacizumab (Avastin; Genentech, Inc, South San Francisco, Calif); and 1, 852A (an experimental m-toll agonist).

Tumor Characteristics

Per our final histologic evaluation of the MLN specimens, no obvious features distinguished the asynchronous metastases from a typical RCC pattern (Figure 2). The median Fuhrman grade[8] was 3 (range 2–3) (Table 1). Minimal necrosis was seen in the MLNs; however, we noted uniform angiolymphatic invasion.

Survival

From the University of Minnesota Cancer Center Registry, we were able to gather complete data on 155 patients with RCC who were diagnosed, treated, and followed up at our institution. The overall survival time of the patients with stage I, II, and III disease at our institution did not significantly differ, so to increase the power of our subsequent analyses, they were grouped together. Patients were thus stratified into 3 categories for our survival analysis: stage I to III (part of the control group, n = 108), stage IV (part of the control group, n = 38), and resection of MLN metastases (ie, metastasectomy; our study cohort, n = 9). Detailed information on patient characteristics, tumor stage, and survival of these 3 groups is provided in Table 3.

From the time of initial diagnosis of MLN metastases, our study cohort had a significantly higher survival (log–rank test, $P < .0001$) than did patients with stage IV disease treated at our institution (Figure 3, *A*). Similarly, from the time of resection of MLN metastases, our study cohort had a significantly higher survival (log–rank test, $P = .021$) than did patients with stage IV disease who were treated at our institution (Figure 3, *B*).

For final analysis, we extracted 2 subsets to compare with our study cohort.

Because no directly analogous group of patients with isolated asynchronous MLN metastases who did not undergo resection of metastases was available, we selected these 2 subsets: (1) patients with lung parenchymal lesions who underwent resection of metastases and (2) patients who had stage IV disease with pulmonary metastases when they first came to our institution and who did not undergo resection. From the time of resection (for both our study cohort and the subset with resectable lung parenchymal lesions), the survival was higher (log–rank test; $P = .0025$) than for the subset with unresectable pulmonary metastases (Figure 3, *C*). The survival

TABLE 3. Patient and tumor characteristics, by group (per Registry)

	Stage I to III	Stage IV	MLN metastasectomy (study cohort)	P*
No. of patients	108	38	9	
Race				.67
White (%)	81.5%	81.6%	88.9%	
Black (%)	2.8%	10.5%	0%	
Other (%)	15.7%	7.9%	11.1%	
Sex				.13
Male (%)	60.2%	76.3%	77.8%	
Female (%)	39.8%	23.7%	22.2%	
Age (y)	55.8 ± 15.9	58.6 ± 11.2	58.3 ± 11.9	.47
Survival after initial treatment				0.001
1 year (%)	95%	55%	100%	
2 years (%)	90%	37%	100%	
3 years (%)	87%	30%	80%	
4 years (%)	83%	20%	80%	
5 years (%)	77%	20%	80%	
Mean (y)	4.2 ± 0.12	1.8 ± 0.23	3.9 ± 0.14	
Median [range] (y)	> 6.4 [0.02– >6.4]	1.04 [0.1–5.7]	>23.5 [3.9–>23.5]	

MLN, Mediastinal lymph node. *Analysis between groups.

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did not significantly differ between our study cohort and the subset with lung parenchymal lesions. The median survival time from the time of resection for the subset with lung parenchymal lesions that were resectable (Figure 3, *C,* "lung metastasectomy) was 4 years (range, 2.07–> 6.5). For the subset with lung parenchymal lesions that were not resectable (Figure 3, *C,* "stage IV–lung") the median survival from time of initial treatment was 1.02 years (range, 0.1–5.6). Again, for our study cohort, MLN metastasectomy, the median survival from time of resection was 3.2 years (range, 2.8–> 3.2). The Motzer score for the subset with lung parenchymal lesions was 0.83 ± 0.86, and for the subset of patients with stage IV disease with pulmonary metastases, 0.81 ± 0.75.

Discussion

Prognosis

Histologic analysis of RCC specimens provides insight into the propensity for local–regional recurrence and metastases. Papillary tumors have a tendency toward local–regional recurrence with local lymph node invasion. However, tumors with a clear cell variant have a tendency toward vascular invasion; consequently, patients often present with distant metastases.[8,9] In our study cohort, the predominant cell type was a clear cell variant.

In addition, the tumor grade provides prognostic information. In 1982, Fuhrman, Lasky, and Limas[8] established a grading system (1 through 4) based on increasing nuclear size, cellular irregularity, and nucleolar prominence, that correlates with the survival. Other investigators have confirmed the association between increasing grade and worsening survival.[10-12] In particular, a larger tumor size (>8 cm) and a higher number of mitoses per 10 high-power fields (>1) correspond to a worse survival.[12] In our cohort of 9 patients, all demonstrated angiolymphatic involvement, not entirely unexpected given metastatic lymph node disease.

Motzer and associates developed a simple prognostic scoring system for patients with RCC and asynchronous disease. Patients receive a score of 0 to 3 on the basis of the presence of each of the following risk factors (1 point for each risk factor): low Karnofsky performance status (<80), anemia (hemoglobin ≤13 g/dL for men and ≤11.5 g/dL for women), and hypercalcemia (serum calcium >10 mg/dL). Patients with no risk factors have a 25% 3-year survival. Patients with 1 risk factor have an 11% 3-year survival, and those with 2 or 3 risk factors, a 0% 3-year survival.[3] In our study cohort (Table 1), only 1 patient (male) had anemia (Motzer score of 1). All other patients had a score of 0. On the basis of this scoring system, our study cohort had a good prognosis. Of interest, lymph node involvement has been associated with a worse survival.[6,7,10,11]

Most RCC recurrences or metastases occur within 5 years after initial treatment; patients who are disease-free at 5 years are traditionally considered to be cured. Although isolated asynchronous metastases developed within 7 years after radical nephrectomy in most of our 9 study cohort patients, in 1 patient metastases developed 23 years after radical nephrectomy. This patient had a low Furhman grade and a low Motzer score, likely indicative of the indolent nature of that particular tumor.

Resection of Metastases

Because resection of synchronous metastases does not impart a significant survival advantage,[4] patients with stage

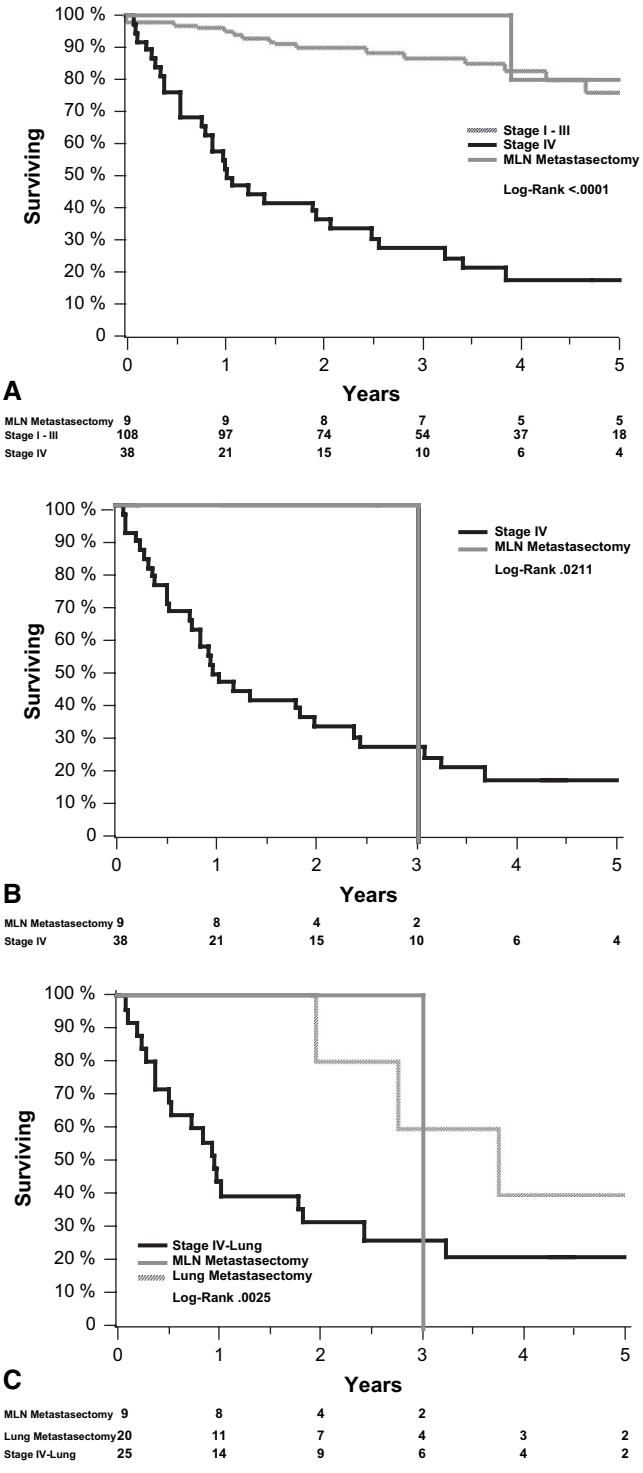

Figure 3. A, Per the University of Minnesota Cancer Center Registry, RCC and stage-specific overall survival time for the MLN metastasectomy cohort stage I, II, or III versus stage IV. B, Overall survival for patients with stage IV disease from the time of diagnosis versus our study cohort from the time of resection of metastases. C, Overall survival for patients with stage IV RCC with pulmonary metastases on presentation from the time of their diagnosis to the survival from the time of metastasectomy for the MLN metastasectomy and lung parenchymal metastasectomy cohorts. Above the *abscissa,* censored Kaplan–Meier survival curve, with log–rank analysis and the number of patients at risk. *RCC,* Renal cell carcinoma; *MLN,* mediastinal lymph node.

IV RCC are usually treated with either palliative or experimental chemotherapy or with radiation therapy. Often, patients with isolated asynchronous metastatic disease are erroneously treated like patients with synchronous metastatic disease. However, the 2 groups have different prognoses and different responses to treatment. Possibly because of differences in tumor burden, patients who have RCC with asynchronous RCC metastases have a more favorable prognosis (median survival, 21 months)[2] than patients with synchronous metastases (median survival, 10 months).[3] Furthermore, evidence is accumulating regarding the efficacy of resection of metastases.

Cytoreduction through complete resection of locally recurrent RCC[13] or asynchronous metastases[5,7, 3-15] improves the patient survivals. Resection of lung parenchymal metastases is feasible[6,7,16,17] and improves survival time (median, 35 months).[4,6,7,16] Furthermore, unlike resection of locally recurrent RCC, which often requires extensive intra-abdominal resection,[15] resection of pulmonary metastases is associated with minimal morbidity.[4,6,7]

Thus far, 1 previous case report has been published describing resection of RCC MLN.[18] In that report, from Japan, the patient survived at least 6 years after resection of metastases. In our series of 9 patients, we have now demonstrated that resection of metastases can be performed safely via thoracotomy or thoracoscopy with a brief hospital length of stay, with minimal morbidity, with no postoperative mortality, and with excellent long-term results. In skilled hands, a thoracoscopic approach is adequate. At both a median and mean follow-up period of 3.2 years, of our 9 patients, 7 were alive and well. These 7 patients had a significantly longer survival time (mean, 47 months) than other patients with stage IV disease treated at our institution.

Chemoradiation, Tumor Vaccines, and Cytokine Therapy

In general, all patients with RCC are treated with a nephrectomy. For stage I and II, this could be a simple nephrectomy or a radical nephrectomy (the standard for stages III and IV). Limited clinical data are available for the use of standardized chemotherapeutic regimens for patients with advanced RCC.[19] However, the use of IL-2 and interferon-alpha was associated in one study with a response rate of around 15%.[20] In other studies, a tendency to relapse was noted in patients treated with IL-2 alone, whereas relapse was less likely in patients who underwent cytoreduction via resection

of metastases (ie, metastasectomy) and subsequent IL-2 therapy with a complete response.[14,21]

Recently, novel chemotherapeutic agents have been added to the standard regimen for patients with metastatic RCC: sorafenib in December 2005 and sunitinib in January 2006. Two additional agents, far along in clinical phase trials, show potential: bevacizumab, an antibody against vascular endothelial growth factor, and temsirolimus, a mammalian target of rapamycin inhibitor.

The large multivalent immunogen vaccine, an autologous vaccine strategy developed at the University of Minnesota, continues to be experimental. Additionally, 852A, an m-toll agonist, and cetuximab, an antibody against epidermal growth factor receptor, are both experimental agents that currently are used at our institution as part of another protocol. At the time of RCC recurrence, cytokine therapy with high-dose IL-2 can be used (if not used before); sunitinib or sorafenib can be employed.

Sunitinib, a small molecule receptor tyrosine kinase inhibitor, has a possible mechanism of action through the vascular endothelial growth factor receptor. Sorafenib, a small molecule inhibitor of the Raf kinase, potentially works through the vascular endothelial growth factor receptor as well as platelet-derived growth factor. Both chemotherapeutic agents target vascular invasion.

Conclusion

Most patients with RCC who have a 5-year disease-free interval are considered cured, but our series of 9 patients demonstrated that MLN metastases can occur more than 20 years after initial treatment. Consequently, long-term surveillance may be required to appropriately monitor patients with RCC. Resection of isolated asynchronous MLN metastases is safe and may offer a survival advantage; such patients should be offered careful surgical evaluation for resection of metastases.

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